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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
ANDRES, JANET L	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/971,708
Filing Date: October 09, 2001
Appellant(s): SHU ET AL.

Richard Lebovitz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 22 September 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences that will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Celis, J., et al. FEBS Lett. vol. 480, 2000, pp. 2-16.

Dodolet, V., et al., "Eph receptors and ephrin ligands: embryogenesis to tumorigenesis" Oncogene, vol. 19, 2000, pp. 5614-5619.

Robinson, D. et al., "The protein tyrosine kinase family of the human genome" Oncogene, vol. 19, 2000, pp. 5548-5557.

Streit, M., et al., "Adhesion receptors in malignant transformation and dissemination of gastrointestinal tumors" J. Molecular Medicine, vol. 74, 1996, pp. 253-268.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 22-24 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" use for the claimed invention. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966):

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

These claims are drawn to a method of detecting KSE132/EphA6 in pancreas cells. The specification, however, fails to provide a specific and substantial asserted utility for either the protein or methods of detecting it in pancreas cells. While applicant states that the protein is found in the pancreas and thus aberrations would lead to developmental pancreatic disorders (p.

4), the specification does not disclose any disorders known to be associated with it. Merely indicating a possibility is not sufficient to identify or confirm a "real world" context of use; clearly further research would be required to identify a disorder in which the protein is involved. Thus, further research is required to identify a utility for its detection in pancreas cells. There is no benefit in knowing whether the protein is there or not, since nothing is known about its function or the significance of its presence. See Brenner v. Manson, noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

The invention also lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. KSE132 is a tyrosine kinase receptor that is also known as EphA6. Eph receptors are generally known in the art to be involved in cell sorting during development (Dodelet et al., Oncogene, 2000, vol. 19, pp. 5614-5619). However, there is no specific and substantial utility associated with this general role; there are no teachings in the art as to how a method of identification of an Eph receptor, and particularly as to how a method of identification of EphA6, could be used for any specific purpose. That members of a class of proteins appear to have roles related to development fails to teach what those roles are, or how any particular member of the family or method of identifying it could be used.

Claims 22-24 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

1. Well-established utility of ephrins (Ephs):

Appellant argues that ephrins have a well-established utility as signaling molecules in physiological and developmental processes. Appellant states that 546 articles, 23 issued patents, and 160 published patents describe or mention ephrins. Appellant states that ephrins are a well-known class of molecules and that they play functional roles in development, particularly in pattern formation and morphogenesis. Appellant adds that EphA6 is a tyrosine kinase. Appellant argues that the Examiner has provided no evidence to rebut these positions. Appellant argues that the specification clearly teaches how to identify EphA6. Appellant states that it is not necessary to show disease association since such association is not required by statute and not the only means by which utility can be established. Appellant argues that Eph6A has been detected in developing and adult cochlea and that EphA6 is analogous to the glial example in the Written Description Guidelines.

Appellant's arguments have been fully considered but have not been found to be persuasive. To clarify, EphA6 is not an ephrin, it is an eph; this error appears in the amendment of 30 March 2004 and in the office action of 14 June 2004. Eph receptors interact with ephrins (Dodelet et al., p. 5615, figure 1). While they are in fact a well-known class of molecules, they have no common function that would endow a member of that class, or of a method of detecting it in a particular tissue, with a utility. What is known about ephrins and ephs is that they control directional movement of cells and neuronal growth cones during development (Dodelet et al., p. 5614, column 1, p. 5615, column 2). It is clear that the interactions of various ephs with their various ligands are important in development. Some are also expressed in cancer (Dodelet et al.,

p. 5616, column 2); however neither Dodelet et al. nor Appellant provide any indication that EphA6 is. This general knowledge of the role of ephs and ephrins is not sufficient to provide any particular eph or a method of detecting it with a utility. On learning that a molecule was a member of the eph family, the artisan would know that it was probably somehow involved in directional movement of cells during development. The artisan would not, however, know any more than that. There is no particular role associated with the identification of a molecule as an eph. There is only the indication that it is somehow involved in cell migration during development. As was stated in the office actions of 25 July 2003, 5 January 2004, and 14 June 2004, further research would clearly be required before the artisan would know how to use a method of identifying such a molecule in pancreatic cells.

That EphA6 is a tyrosine kinase further fails to provide it with a well-established utility. As was stated in the office action of 5 January 2004, there are many different tyrosine kinases with many different substrates and many different functions. Robinson et al. (Oncogene, vol. 19, 2000, pp. 5548-5557) teaches that protein tyrosine kinases are a "large and divergent family" (p. 5548, column 1). The family includes both receptors and non-receptors (pp. 5550 and 5551, tables 2). Robinson et al. states (p. 5548, column 1) that they are involved in growth, differentiation, adhesion, motility, and death. There is no thus utility that is readily apparent from the identification of a molecule as a tyrosine kinase; their functions are varied. Thus there is no utility that is readily apparent for detecting such a molecule in pancreas cells.

Appellant's statement that the specification teaches a means of identifying EphA6 appears to result from a misreading of the Examiner's comments. The specification clearly does

teach a method of identifying EphA6; what was stated was that no utility for the method was provided, for the reasons set forth above.

While an association with disease is not required by stature and there are many other means by which utility can be established, utilities such as drug discovery, detecting, diagnosing, monitoring, prognosticating, preventing, and treating disease are what are set forth in the specification (p. 2, lines 2-6, p. 4, lines 2-10, and throughout, see for example p. 16, lines 25-30 and p. 17, lines 7-19). Thus these are the utilities that have been addressed by the Examiner. Other proposed utilities (p. 2, lines 9-12) do not appear to be applicable to a method of detecting Eph6A in pancreas cells.

That EphA6 has been detected in cochlea provides no guidance as to how a method of detecting it in pancreas cells can be used. As stated above, the artisan would recognize that the protein was somehow involved in development and cell migration, but this general knowledge would not provide a method of detecting the protein in pancreas with a well-known or readily apparent use. Further, as stated in the office action of 14 June 2004, example 6 of the written description guidelines does not specifically address utility. However, the glial protein provided in this example is both specific to glial cells and associated with differentiation of those cells. It was found to be useful to identify agents that regulated differentiation and that thus would be of interest in therapy for gliomas. No such role in pancreatic development is provided for the instant protein.

2. Kinase activity:

Appellant argues that EphA6 is a tyrosine kinase and that enzyme activity is sufficient to satisfy the utility requirement. Appellant cites example 8 of the utility training guidelines and

Cross v. Iizuka. Appellant argues that ephrin receptors have a characterized kinase activity, citing the teachings of the specification that they behave similarly to other tyrosine kinases receptors.

Appellant's arguments have been fully considered but have not been found to be persuasive. As was stated in the office action of 5 January 2004, that the polypeptide is an enzyme does not endow it with a utility. There is no particular function associated with EphA6; thus, labeling substrates for use in assays would be useful only to investigate the function of the protein itself. The hypothetical enzyme referred to in example 8 of the guidelines is a "well-known tyrosine kinase" and the example further assumes that the substrates are well known. There are, however, many different tyrosine kinases with many different substrates and many different functions (Robinson et al., cited above); merely identifying a protein as having this activity does not provide any information as to what it does or how it could be used. Similarly, Cross v. Iizuka deals with inhibitors of thromboxane synthetase, a well-known enzyme with a particular known function. MPEP §2107.01 discusses utility guidelines in general and cites Cross v. Iizuka; none of the cited references indicate that enzymatic activity alone, absent any known use for that activity, is sufficient to endow the protein that possesses it with a utility. Thus, there is no specific and substantial utility associated with the protein or with its detection in a particular cell type. The function of the protein is not known, it is not known to be associated with any disease, and thus there is no benefit to be gained from detecting its presence.

3. Tissue specificity:

Appellant argues that EphA6 is highly restricted to brain, pancreas, and testis. Appellant argues that the pancreas is in the somatic compartment, which is distinct from the reproductive

compartment and from the brain. Appellant argues that the method could be used to detect metastatic pancreatic cells. Appellant argues that the statement that tissue specificity is not specific to the molecule is a *per se* rule. Appellant argues that tissue specificity was published by the office to be an adequate utility. Appellant states that example 12 of the utility guidelines describes a cancer marker. Appellant argues that the differential expression of EphA6 in brain and testis is a specific property of the protein. Appellant states that example 6 of the written description guidelines did not provide direct evidence that the glial cell marker was involved in differentiation and that this conclusion was based solely on homology. Appellant again refers to the statement that the mouse homologue of EphA6 is found in the cochlea and that it would be reasonable to infer that EphA6 had the same function. Appellant concludes that the office is applying a double standard. Appellant additionally argues that it is reasonable to expect that expression of RNA would lead to expression of the encoded protein, and that any deficiency in this conclusion would apply to example 6 of the written description guidelines as well.

Appellant's arguments have been fully considered but have not been found to be persuasive. Both testicular cancers and gliomas can metastasize outside of their "compartments", although gliomas do so rarely. Thus, detection of EphA6 outside of the pancreas, testis, or brain would not be indicative of the presence of a pancreas cell. The cells expressing EphA6 could be from a metastasized testicular cancer or glioma. Furthermore, Appellant provides evidence only that EphA6 is present in normal prostate cells. There is no guidance to indicate that it would be present on metastasizing cells, which no longer have the intercellular associations of the pancreas. While no particular function can be assigned to EphA6 based on its identification as an eph, what can be discerned, as stated above, is that it is involved

in cellular interactions and thus it cannot be assumed that its levels would be the same in pancreas cells that have metastasized and are no longer in their normal environment. Levels of cell surface proteins frequently change in metastasis. See, for example, Streit et al. (J. Molecular Medicine, vol. 74, 1996, pp. 253-268), which teaches that integrin adhesion receptors are altered during malignant transformation of pancreatic cells (p. 260, column 1), and that down-regulation of the cell-surface protein E-cadherin can result in dedifferentiation and invasiveness of these cells (p. 260, column 2). Thus further research would be required in order to determine whether the method could actually be used to detect metastasizing pancreatic cells, since it is not known whether these cells would express EphA6.

A specific utility is one that is, according to the guidelines, specific to the subject matter claimed, as contrasted with a general utility that would be applicable to the broad class of the invention. In the context of method of use of detection of the protein in order to detect pancreas cells, it is agreed that the utility is specific to EphA6. However, the utility must not only be specific, it must be substantial, that is, "real world", as required on p. 6 of the guidelines. As stated on p. 6, "[u]tilities that require or constitute carrying out further research to identify or reasonable confirm a "real world" context of use are not substantial utilities. For the reasons set forth above, further research would clearly be required to "reasonably confirm" a use for EphA6 in detecting metastatic pancreas cells; it is not even know if the protein is present in such cells. As stated in the office action of 14 June 2004 (p. 4), the example presented in the utility guidelines, example 12, provides this substantial utility. The hypothetical protein is known to be differentially expressed on melanoma cells as opposed to normal skin cells and can clearly be used to identify such cells. The guidelines indicate that such differential detection would be

useful; no further research is required. Appellant states that there is no reason why tissue specificity for normal tissue would not provide a similar utility. However, Appellant states that EphA6 is found in brain and testis cells also. Therefore detection in a cell does not indicate that the cell is a pancreatic cell. Furthermore, Appellant also argues that the assay can be used to detect metastatic pancreatic cells, which would indicate that it is not specific for normal cells. Thus, as stated above, further research is required in order to determine what types of cells can be detected and whether there is utility associated with such detection.

Appellant refers again to example 6 of the written description guidelines. It is noted that that example was found to lack written description. It is also noted that utility is not directly addressed. The guidelines do not state what aspect of the invention is considered to provide it with a utility. Regardless, what is stated is that the cDNA fragment is obtained from a glioblastoma library and is homologous to a known molecule that is associated with glial cell differentiation. It is further stated is that the encoded protein would be expected to be involved in glial cell differentiation and the molecule is useful as a probe for glial-specific receptors. By contrast, the instant protein, EphA6, is homologous only to a general class of proteins that are only generally associated with cell movement. It is not homologous to a protein known to be involved in anything in pancreatic, glioma, or testis cells. For the reasons stated above, there is no utility associated with detecting the protein itself. The fact patterns are different and there is no double standard.

Appellant states that any deficiency in the correlation between RNA and protein expression would apply to example 6 as well. It would not; example 6 discusses identification of nucleic acids only. Furthermore, while Appellant states, citing Alberts et al., that "transcription

usually predominates", the art teaches that the correlation of protein expression to message expression is more complex. Celis et al. (FEBS Lett. vol. 480, 2000, pp. 2-16) states that only a limited number of studies have been performed comparing the results of DNA and protein assays (p. 13, column 1). While Celis et al. describe a study that reports a "good" correlation, Celis et al. also states that discrepancies exist, as had been reported by a previous study (p. 13, column 1). Thus it cannot be assumed that the presence of mRNA would be predictive the presence of a protein. Appellant has provided a single experiment in which the message levels are not quantified and in which no protein levels are presented. This is not sufficient information to predict that the protein is indeed present in pancreatic cells and can be detected, as would be required for Appellant's invention to function.

Thus, because there is no well-established utility associated with the identification of a molecule as an eph, and since there is no specific and substantial utility associated with identifying EphA6 in pancreas cells, the invention lacks utility under 35 U.S.C. 101. Further, since the invention lacks utility, the artisan would not know how to use it, and the specification fails to enable the invention as required under 35 U.S.C. 112, first paragraph.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Janet L. Andres, Ph.D.
November 23, 2004

Conferees
Brenda Brumback

Jeffrey Siew

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

ORIGENE TECHNOLOGIES, INCORPORATED
6 TAFT COURT
SUITE 100
ROCKVILLE, MD 20850

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600